REMARKS

Claims 1, 2 and 4-15 are stated to be pending in this application. Claims 1, 2 and 4-15 are stated as having been rejected. Applicants respectfully point out that claim 4 was previously canceled and is no longer pending in the instant application. Therefore, claims 1, 2 and 5-15 are properly rejected. Claim 1 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

The rejection of claims 1, 2 and 5-15 under 35 U.S.C. 103(a) as being unpatentable over Ojwang et al. (1997), in view of Taylor et al. (1999) and Baracchini et al. (US Patent 5,801,154) has been maintained for reasons of record. The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to target the listed region of TNRF1 with antisense and then incorporate the claimed modifications as taught by Baracchini et al. since Baracchini et al. teach that the coding region, of which the claimed target region is part, is taught to be a desirable target. The Examiner suggests that one of skill would have been

motivated to modify the oligonucleotides of Ojwang et al. because they teach the desirability of such modifications and that TNFR1 is a mediator of inflammation and an attractive target for intervention. The Examiner suggests that an expectation of success is provided by Taylor and Baracchini et al. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to recite that the antisense compounds of the instant invention are ones targeted to specific nucleobase regions within the coding region of SEQ ID NO: 1. Support for this amendment to the claims can be found at Table 1 of the specification where effective target regions are identified beginning at nucleobase 727 and ending at nucleobase 748 (see page 58, line 25), and beginning at nucleobase 899 and ending at nucleobase 971 (see page 58, line 46).

Ojwang et al. (1997) disclose that antisense oligonucleotide inhibition of TNFR1 is a useful tool in understanding the role of this protein in cytokine induction and cell proliferation. The paper discloses partial phosphorothioate antisense deoxyoligonucleotides containing C-5 propynyl or hexynyl derivatives of 2'-deoxyuridine which caused attenuation of TNFR1 mRNA and protein and inhibited TNF-alpha-induced expression of IL-6

in MRC-5 cells. The oligonucleotides were targeted to the poly (A) signal site of TNFR1 mRNA while a uniform phosphorothioate oligonucleotide targeted to the translation initiation codon of TNFR1 had no effect. This paper fails to teach or suggest antisense compounds as claimed which are targeted to specific nucleobase regions of SEQ ID NO: 1. Therefore, this primary reference fails to teach the limitations of the claims as amended.

The secondary references cited fail to overcome the deficiencies in teaching of the primary reference, either alone or when combined with the primary reference.

Taylor et al. (1999) is a review paper on the technology of antisense that describes its uses in functional genomics. Although the paper teaches the use of antisense in general, nowhere does this paper teach or suggest that antisense compounds targeted to a specific nucleobase region within a coding region of TNFR1 could be successfully used to inhibit expression of this particular gene.

Baracchini et al. (US Patent 5,801,154) teach methods of modifying antisense oligonucleotides to enhance activity. However, nowhere does this patent teach or suggest antisense oligonucleotides as claimed targeted to a specific region within the sequence of TNFR1 of SEQ ID NO: 1, or any region of such a

nucleic acid molecule. The mere teaching of the coding region as being a general target for antisense does not provide one of skill with the knowledge to target successfully the specific regions as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims, which claim antisense compounds targeted to specific regions of a specific SEQ ID NO., and thus cannot render the instant claimed invention obvious. Further, the reference of Ojwang et al. teaches that use of one oligonucleotide targeted to the beginning of the coding region is without activity, thus providing one of skill with doubt about success with other oligonucleotide targeted to the coding region. It is only with the specification in hand that one of skill would understand how to make and use the claimed antisense, in particular

what region of the gene to target with antisense as now claimed. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 102/103

Claims 1, 2, 12 and 14 have been rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Draper et al. (US Patent No. 5,514,577). The Examiner suggests that this patent discloses a sequence that possesses 100% identity with residues 1257 through 1266 of SEQ ID NO: 1 and would thus inherently hybridize with and inhibit expression of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Draper et al. disclose a sequence that is complementary with nucleobases 1257 through 1266 of SEQ ID NO: 1 of the instant application. As discussed *supra*, Applicants have amended claim 1, and by dependency claims 2, 12 and 14, to recite that the compounds of the instant invention are targeted to regions that do not include nucleobases 1257 through 1266. In order to anticipate or make obvious a claim the cited reference must teach all the limitations of the claims (MPEP 213 and 2143). Accordingly this reference cannot anticipate or make obvious the claims as amended. Withdrawal of this rejection is therefore respectfully requested.

Claims 1, 2, 12 and 14 have been rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Le et al. (US Patent No. 5,656,272). The Examiner suggested that this patent discloses a sequence with 100% identity with residues 835 through 852 of the instant application and thus would specifically hybridize with TNFR1 of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Le et al. disclose a nucleic acid molecule that is complementary to a region within SEQ ID NO: 1, from nucleobases 835 through 852. As discussed *supra*, Applicants have amended claim 1, and by dependency claims 2, 12 and 14, to recite that the compounds of the instant invention are targeted to regions that do not include nucleobases 835 through 852. In order to anticipate or make obvious a claim the cited reference must teach all the limitations of the claims (MPEP 213 and 2143). Accordingly this reference cannot anticipate or make obvious the claims as amended. Withdrawal of this rejection is therefore respectfully requested.

III. Double Patenting

Claims 1, 2 and 5-16 have been rejected under the judicially created doctrine to obviousness-type double patenting as being

unpatentable over claims 1-11 of U.S. Patent 6,007,995. The Examiner suggests that although the conflicting claims are not identical, they are not patentably distinct. Applicants are filing herewith a terminal disclaimer as required under 37 CFR 1.321(c). Accordingly, withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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